IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

FERGUSON, Mark W.J. Atty. Ref.: 39-288; Confirmation No. 6683

Appl. No. 10/654,994 TC/A.U. 1647

Filed: September 5, 2003 Examiner: Romeo, D.S.

For: PHARMACEUTICAL COMPOSITION CONTAINING AN ACTIVIN OR INHIBIN STIMULATOR

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION

I, Abdul Sattar, do hereby declare and state as follows.

1. I hold the position of Translational Pharmacology Manager at Renovo Limited, Manchester, United Kingdom and have held that position for approximately 7½ years.

2. I have reviewed U.S. Application No. 10/654,994, the Office Action dated December 28, 2007 that issued in connection with that application, and the Amendment that was filed May 28, 2008 in response to the December 28, 2007 Office Action. I understand that, in the December 28, 2007 Office Action, the Examiner rejected the claims then pending as being unpatentable over Mitrani (U.S. Patent 5,753,612) (herein

after "Mitrani"), or Mitrani in view of Ferguson (WO 92/17206), Hayashi (US Patent 5,145,680) or Ferguson (GB 2 265 319 A), and also as unpatentable over De Kretser (U.S. Patent 5,196,192), or De Kretser in view of Ferguson (WO 92/17206).

On page 7 of the December 28, 2007 Office Action, the Examiner stated:

> Furthermore, there has been no direct comparison of the application of the doses of exogenous activin suggested by Mitrani with the doses of exogenous activin taught in the examples of the present application.

3. The study described in paragraphs 4 and 5 below was undertaken to compare the effects of administration of activin at doses recited in the claims of U.S. Application No. 10/654,994 as presented in the May 28, 2008 Amendment (hereinafter, "the claims now pending") with the administration of activin at doses considered by Mitrani. This study was conducted at my direction and under my supervision.

The doses of activin considered in Mitrani are defined with reference to the amount of activin administered per kilogram of body weight, and not with reference to amount per unit length of the site to be treated (as per the claims now pending in U.S. Application No. 10/654,994). While it is not possible to directly compare the doses considered in Mitrani to those recited in the claims now pending in U.S. Application No. 10/654,994, the doses considered by Mitrani appear to be generally much higher than those recited in the claims now pending in U.S. Application No. 10/654,994.

The circumstance in which the higher doses considered in Mitrani can most closely be made to approximate those considered in the claims now pending in U.S. Application No. 10/654,99 would occur if a patient with a relatively low body weight

were treated with the lowest dose disclosed in Mitrani (thus giving rise to a low total dose of activin administered), while at the same time possessing relatively long wounds requiring treatment (meaning that the low total amount of activin was provided in respect of a long length of wound).

The lowest dose of activin considered in Mitrani is 0.001mg/kg (i.e., 1000ng activin/kg body weight). The average female human is lighter than a male, and has a body weight of approximately 70kg. Thus, an average female human given the lowest dose considered in Mitrani would receive a total of 70,000ng of activin.

The longest wounds that will generally be treated in a human patient to reduce scarring are those associated with breast reduction or augmentation. These may be up to about 35cm long. Thus, in the case of a female patient undergoing bilateral breast reduction, the total wound length to be treated might be up to 70cm.

Based on these calculations, it can be seen that, even in relatively extreme circumstances (lowest suggested dose, light patient, very large wounds) conversion of the lowest dose considered in Mitrani to the format of "amount of activin/centimetre wound length" would call for administration of 70,000ng of activin to a patient with 70cm of wounds, a dose of 1000ng of activin per centimetre of wound to be treated.

It is in light of these calculations that the effects of exogenous administration of activin at a dose of 1000ng/cm of wound have been investigated, in order that this administration might be compared with the doses recited in the claims now pending in

U.S. Application No. 10/654,994 (represented by administration of 2.5ng/cm of wound or 5ng/cm of wound).

4. The methods used in the study were as follows.

Activin (R&D systems, batch number BNV17) was dissolved in phosphate buffered saline (PBS) to produce injectable solutions described further below.

Male Sprague Dawley rats (200-250g) were anaesthetised, partially shaved and marked with sites for formation of 1cm experimental wounds (two wounds per animal, each 1cm wound being formed 5cm from the base of the skull and 1cm from the mid line of the animal). Sites where wounds were to be formed were provided with either a controlled injection (100µl PBS) or a 100µl injection of a medicament providing 2.5ng activin, 5ng activin or 1000ng activin. These injections gave rise to a raised bleb, which was then immediately incised to form the 1cm experimental wound. All wounds were then re-injected one day post-wounding with the appropriate treatment (control or activin doses as discussed above) via injection of 50µl to each of the two margins of the 1cm wound.

The macroscopic appearance of scars produced on healing of the experimental wounds was assessed after 70 days post-wounding. The appearance of the scars was rated using a visual analogue scale (VAS) in which 0 represents unwounded skin, and 10 severe pathological scarring. A reduction in scarring thus gives rise to treated wounds having a lower VAS score than controls, while an increase in scarring gives rise to treated wounds having a higher VAS score than controls.

5. The results obtained were as follows.

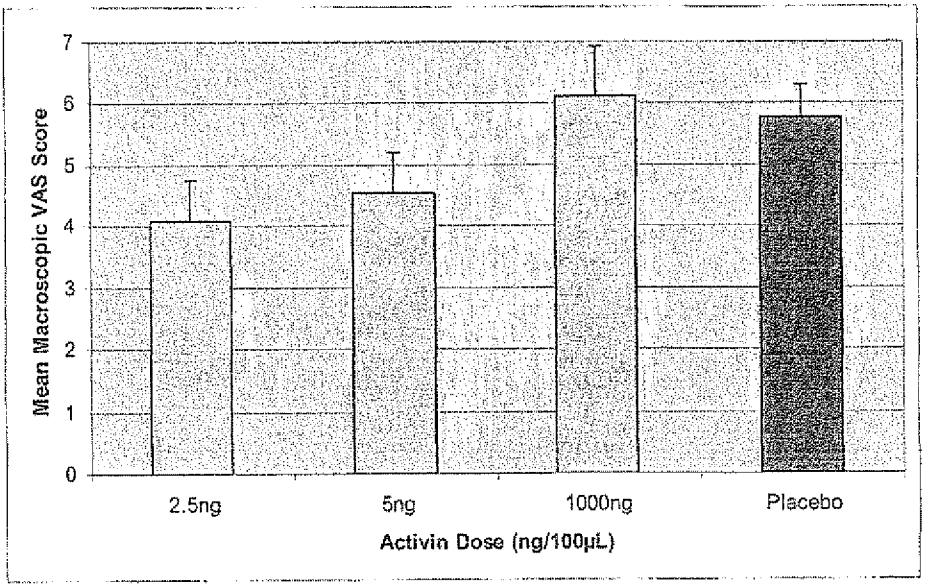
Control wounds (to which only the diluent PBS was administered) gave rise to scars with a mean macroscopic VAS score of 5.8.

Treatment of wounds with activin at a dose of 2.5ng per centimetre gave rise to scars with a mean score of 4.1 on the macroscopic VAS. This value (which is lower than the score for the control wounds) represents a 30% reduction in macroscopic scarring.

Treatment of wounds with activin at a dose of 5ng per centimetre gave rise to scars with a mean score of 4.5 on the macroscopic VAS. This value represents a 22.5% reduction in macroscopic scarring as compared to control wounds.

Wounds treated with activin at a dose of 1000ng per centimetre gave rise to scars with a higher mean macroscopic VAS score of 6.1. Since this value is higher than the controls, it can be seen that administration of activin in accordance with the teachings of Matrani served to exacerbate, rather than reduce, scarring.

These results are shown graphically in the bar chart below.



6. In summary, a dose of 1000 ng activin/cm of wound to be treated does not give rise to the reduction in scarring that is found when using the much lower doses recited in the claims now pending in U.S. Application No. 10/654,994.

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I hereby declare that all statements made herein of my own knowledge are true and that statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Further, declarant sayeth not.

Abdul Sattar

23 June 2008
Date